Are We Adequately Replacing Antibody In Patients With Primary Immunodeficiency?

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Why Be Concerned

- IVIG is Made From Normal Healthy Donors
- Healthy People Have Low Levels of Antibody
- Antibody Titers May Be Falling
  - **Vaccine vs Natural Infection**
    - **Measles**
    - **H. Flu B**
  - **Elimination of "High Risk" Donors**
    - **CMV**
- Higher Levels of Antibody May be Needed for Chronic Infections
- We Know Little of Antibody Titers During Replacement Clinical Studies Have Focused on IgG Levels Rather than Specific Antibody

Issues for Discussion

- Recommended Doses of IVIG have Increased Over the Years
  - What Does that Suggest?
- Antibody Titers in IVIG Preparations
  - Are the in vitro Titers Relevant?
- Do We Know Protective Levels of Antibody?
- Do Current Doses of IVIG Provide Adequate Levels of Specific Antibody?
- Is Any One Else Concerned?

Initial Dose Recommendations

- In the Beginning there was Intramuscular Gammaglobulin
- Immunologists Looked Down, and Said it was Good
- And it Was:
  - Sepsis was Decreased
  - Meningitis was Decreased
  - Severe Pneumonia was Decreased
- Chronic Infections Were Less Responsive
- Efficacy of Gammaglobulin was Accepted by 1957
  - Suggestion that 100 mg/kg/mo > 25 or 50 mg/kg/mo
  - 100 mg/kg/mo Upper Limit of IM Gammaglobulin

Initial Dose Trials

- First IVIG Studies Compared to IM
  - 100 mg/kg for Both
- First Trial of High Dose IVIG
  - 100 mg/kg vs 400 mg/kg
  - No Significant Difference
- Early Study of Dr. Pirofsky
  - 500 mg/kg > 150 mg/kg
  - Especially for Chronic Infection

Comparison of High- vs Low-Dose IGIV in Hypogammaglobulinemia

- Study design
  - **12 patients with hypogammaglobulinemia**
  - **All had chronic lung disease**
    - **PFT >25% below predicted**
  - **12 month crossover: 200 mg/kg vs 600 mg/kg**
  - **No run-in or wash-out periods**
  - **Evaluated incidence of infection**
  - **Measured IgG levels**
  - **Measured pulmonary functions**

Roifman C et al. *Lancet.* 1987;1:1075–1077.

Comparison of High- vs Low-Dose IGIV in Hypogammaglobulinemia

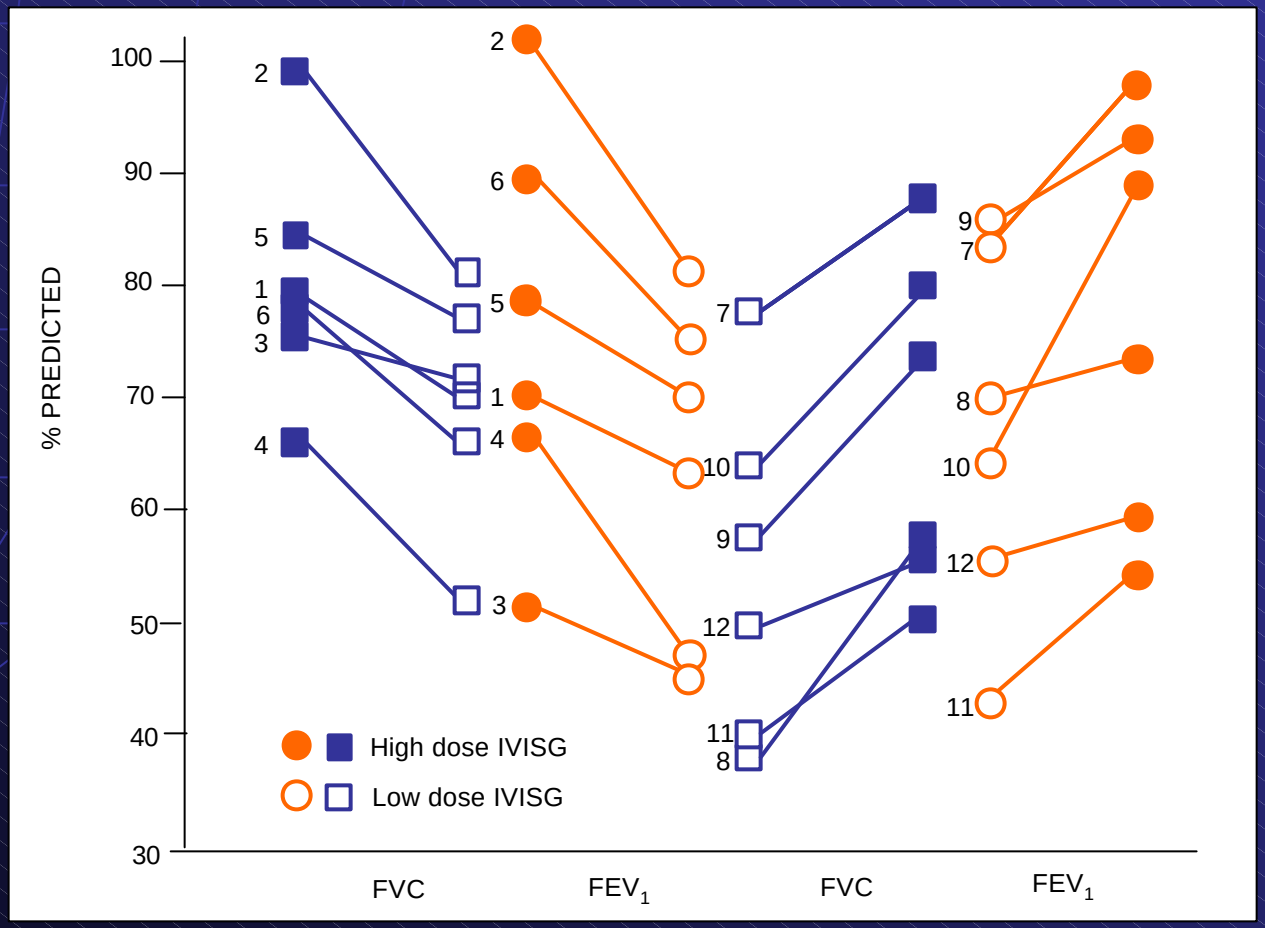
Results – Incidence of Infections

	IgG < 500 mg/dL		IgG > 500 mg/dL	
	Number of episodes	Number of patients	Number of episodes	Number of patients
Upper respiratory	23	12	10	7
Pneumonia	11	8	3	3
Total infections	47	?	15	?

Roifman C et al. *Lancet.* 1987;1:1075–1077.

Comparison of High- vs Low-Dose IGIV in Hypogammaglobulinemia

- Results – Pulmonary Function



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Effect of Different IGIV Dosages in Hypogammaglobulinemia: Overview

Evaluation of dose effect on incidence and duration of infections

Eijkhut H et al. *Ann Int Med.* 2001;135:165–174.

Effect of Different IGIV Dosages in Hypogammaglobulinemia: Results

	Adults/ children (mg/kg)	Infection rate (per patient)	Infection duration	Days to first infection	Serum trough plasma [IgG]
Standard–dose	300/400	3.5	33 days	82	6.5 g/L
Doubled –dose	600/800	2.5	21 days	123	9.4 g/L
		P=0.004	*P*=0.015		

Eijkhout H et al. *Ann Int Med.* 2001;135:165–174.

Effect of Different IGIV Dosages in Hypogammaglobulinemia: Conclusion

- High-dose IGIV significantly reduces the number and duration of infections
- Newly diagnosed patients should first be treated with standard-dose IGIV
- If two or more severe infections occur per year, the dosing regimen should be adjusted to increase plasma IgG level by 1–1.5 g/L
- This cycle may be repeated until a plasma IgG level of ~9.5 g/L is reached

Eijkhout H et al. *Ann Int Med.* 2001;135:165–174.

Effect of Dose
Gamunex vs Gamimune-N

- **Gamunex Group**
  - **4/38 (10.5%) patients receiving > 400 mg/kg**
  - **5/35 (14.3%) patients receiving < 400 mg/kg**
- **Gamimune-N**
  - **(22.6%) patients receiving > 400 mg/kg**
  - **(23.8%) patients receiving < 400 mg/kg**

Roifman etal. International Imunopharmacology 2003; 3:1325-33.

Effect of Trough IgG Level on Incidence of Validated Infections

	Trough IgG Level		
	< 7	7-9	>9 g/L
Gamimune N	**28.6%**	**23.1**	**19.2**
Gamunex	**13.6**	**15.2**	**5.6**
Total	**20.9**	**18.6**	**13.6**

Roifman etal. International Imunopharmacology 2003; 3:1325-33.

Summary of Dose Studies

- Doses of 100 mg/kg Decreased Incidence of Acute, Overwhelming Infections
- Less Effective for Chronic Infections
  - Sinusitis or Lung Disease
- Recent Trials Indicate Increased Efficacy
  - Doses 300-600 mg/kg/month
  - IgG Levels of > 9 gm/L

Implications of Dose Studies

- At Least for Chronic Infections We Need to Provide Higher Amounts of Antibody to Some Organisms
- Don’t Know Which Organisms are Relevant for Patients with Immune Deficiency
- Rely on Data for IVIG Products to Know What Antibodies are Being Provided

Evaluation of Antibody Titers

- Every Product Publishes Tables of Antibody Titers
- A Variety of Assays Used
  - Often Not Relevant to Clinical Use
- Question Whether Titers in IVIG Comparable to Those in Plasma
  - Assays Standardized to Plasma or Serum

ANTI-MICROBIAL ANTIBODY TITERS OF VARIOUS IVIG PREPARATIONS

Antibody Titer	Method	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
CMV	EIA	253 ± 64	110 ± 27	160	246	129 ± 33	283 ± 3
Influenza A	CF	69 ± 13	32	64	181	44 ± 15	96 ± 45
EBV	IFA	5049 ± 3058	2560	6827	5973	1541 ± 205	4907 ± 302
VZV	EIA	1412 ± 174	698 ± 54	1051	1240	833 ± 252	1328 ± 60
Adenovirus	EIA	12 ± 2	6 ± 2	15	9	10 ± 1	7
HSV-1	EIA	43 ± 17	28 ± 9	22	61	34 ± 19	71 ± 11
HSV-2	EIA	34 ± 6	12 ± 2	20	70	13 ± 3	32
Para-influenza-1	CF	16 ± 1	5 ± 5	16	256	13	16
Para-influenza-2	CF	21 ± 8	8	16	136	13	24 ± 11
Para-influenza-3	CF	29 ± 7	8	32	64	18 ± 8	32
Hepatitis A	EIA	17813 ± 1904		14709	17781		
HbsAb	EIA	944 ± 299	952 ± 432	404	802	598 ± 195	1676 ± 917
Aspergillus	EIA	2.6 ± 1.4	0	2.2	0	0	0
M5G-candida	EIA	168 ± 20	237 ± 40	122	181	220 ± 44	107 ± 1
Teichoic Acid		1 ± 2	0	0	0	2 ± 4	0
H. Influenzae b	CF	17691 ± 697	23946 ± 6601	9533	14414	16787 ± 2951	17797 ± 856
Group B Strep	EIA	222 ± 26	261 ± 7	189	189	189 ± 33	154 ± 6
P. aeruginosa A	EIA	7 ± 1	4 ± 1	5	7	2	6
P. aeruginosa B	EIA	29 ± 10	12 ± 4	27	16	9 ± 3	11 ± 1
S.pneumo typ14	EIA	2608 ± 1204	7167 ± 1299	5583	9367	10831 ± 870	6242 ± 1591
S.pneumo typ 18	EIA	17989 ± 4640	20489 ± 1533	12833	18450	8398 ± 2210	4713 ± 6
S.pneumo typ 19	EIA	11106 ± 1210	15906 ± 742	8867	9483	12278 ± 3607	11563 ± 1102
S.pneumo typ 23	EIA	11422 ± 642	15811 ± 2601	9967	9158	17713 ± 3877	10246 ± 3730

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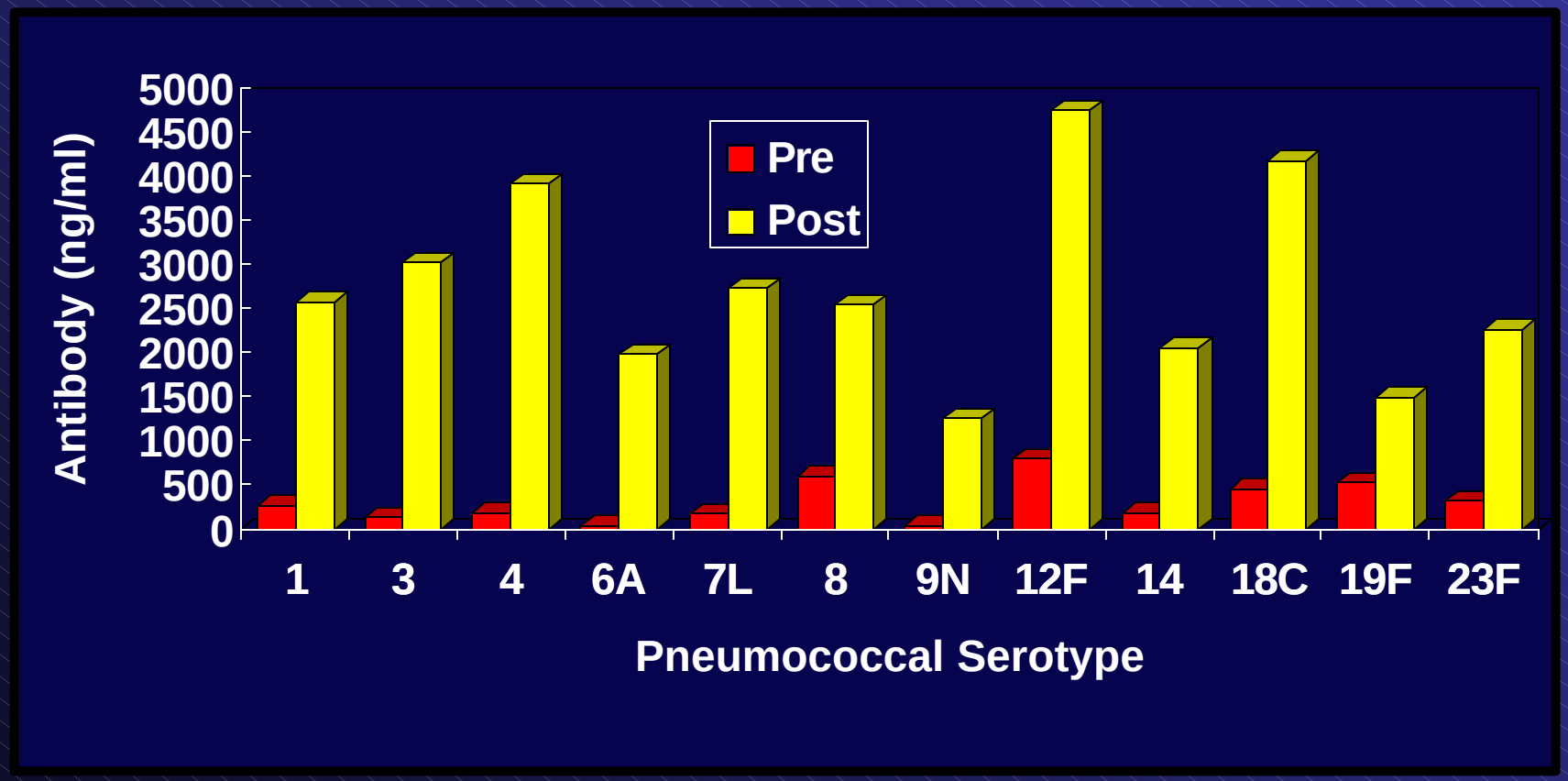
Pneumococcal Antibody Levels in Normal Healthy Adults



Schiffman, G. In: Medical Microbiology, Chapter 6, 1983.

Antibody Titers in Patients

- Virtually Every Clinical Trial Has Evaluated only IgG Levels – Not Specific Antibody
- Few Trials Have Used anti-Tetanus or Anti-Pneumococcal Antibody to Measure Half-Life
  - Did Not Report Actual Levels
- A Few Studies Have Evaluated anti-Pneumococcal Antibody in Patients
  - Used Opsonophagocytosis Assay
  - Suggested Protective Levels in Patients

Anti-CMV Activity of IGIV

- 42 CMV (-) BMT recipients
- 500 mg/kg every 2 weeks. Post-infusion titers below.

Product	Neutralization Titer (plaque assay)	Anti-CMV ELISA (U/mL)
Gamimune N	1:14	1.34
Gammagard	1:43	2.95
Sandoglobulin	1:27	2.27
Polygam	1:26	2.03

Filopovich, L., *et al*, Blood, 1992

Conclusion

- Clinical Data Suggests that Higher Doses of IVIG More Effective for Chronic Infections
  - What Level of Antibody is Protective?
  - What Level of Antibody is Needed When Infected?
- Can We Determine Which Antibodies are Crucial to Improving Efficacy?
  - What are the Most Relevant Organisms?
- Are There Other Ways to Determine Optimal Dose Instead of Clinical Studies?
  - For Example, Antibody to Pneumococcus
- How Can We Address These Issues?